NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED, Plaintiffs, v. TORRENT PHARMACEUTICALS LTD. and TORRENT PHARMA INC., Defendants.	Civil Action No. 17-3186 (SRC)(CLW) (CONSOLIDATED) **OPINION**
TAKEDA PHARMACEUTICAL COMPANY LTD., TAKEDA PHARMACEUTICALS U.S.A., INC., TAKEDA PHARMACEUTICALS AMERICA, INC., and TAKEDA IRELAND LIMITED, Plaintiffs, v. INDOCO REMEDIES LTD., Defendant.	Civil Action No. 17-7301 (SRC)(CLW)

CHESLER, U.S.D.J.

INTRODUCTION

Plaintiffs Takeda Pharmaceutical Company Ltd., Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceuticals America, Inc., and Takeda Ireland Limited (collectively, "Plaintiffs") bring this action for patent infringement against Defendant Indoco Remedies Ltd. ("Indoco") and Defendants Torrent Pharmaceuticals, Ltd. and Torrent Pharma Inc. (collectively, "Torrent.") Plaintiffs own U.S. Patent No. 7,807,689 ("the '689 patent"), which is listed in the Orange Book as protecting Plaintiffs' alogliptin benzoate formulations, marketed under the brand names Nesina®, Kazano®, and Oseni®. Indoco has filed Abbreviated New Drug Application ("ANDA") Nos. 210002 and 209998, seeking approval to market generic versions of Nesina® and Kazano®. Torrent has filed Abbreviated New Drug Application Nos. 21-0159, 21-0160, and 21-0161, seeking approval to market generic versions of Nesina®, Kazano®, and Oseni®. Plaintiffs complain that, by filing these ANDAs with the United States Food and Drug Administration, Defendants have infringed the '689 patent. The parties have stipulated to a finding that the proposed generic products infringe claims 4 and 12 of the '689 patent. A bench trial on Defendants' patent invalidity defenses to infringement was held for 2 days, beginning on November 4, 2019, and ending on November 5, 2019. Upon hearing the evidence presented at trial, this Court finds that Plaintiffs have proven that claims 4 and 12 of the '689 patent are valid and infringed.

STIPULATED FACTS

The parties stipulated to the following facts in the Final Pretrial Order ("FPO"):

12. On June 5, 2019 Plaintiffs and Torrent stipulated that Torrent's submission of its ANDA Nos. 21-0159, 21-0160, and 21-0161 to the FDA and its commercial manufacture, use, offer for sale, sale, or importation of Torrent's

ANDA Products prior to the expiration of the ’689 patent and certain claims therein would constitute literal infringement under 35 U.S.C. § 271 (a), (b), (c), or e(2)(A), if such claims were held valid and enforceable. (ECF No. 81). As a result of the stipulation, the only issue in dispute between Plaintiffs and Torrent was whether claims 1, 3, 4, 9, 11-12, 43, and 49 of the ’689 patent were invalid.

14. On May 7, 2019 Plaintiffs and Indoco stipulated that Indoco’s submission of its ANDA Nos. 209998 and 210002 to the FDA and its commercial manufacture, use, offer for sale, sale, or importation of Indoco’s ANDA Products prior to the expiration of the ’689 patent and certain claims therein would constitute infringement under 35 U.S.C. § 271 (a), (b), (c), or e(2)(A), if such claims were held valid and enforceable. (Case No. 2:17-cv-07301 ECF No. 56). As a result of the stipulation, the only issue in dispute between Plaintiffs and Torrent was whether claims 1, 3, 4, 9, 11-12, 43, and 49 of the ’689 patent were invalid.

16. For purposes of trial, Takeda has agreed that it intends to assert only two claims of the ’689 patent -- claims 4 and 12 —against Defendants. Thus, claims 4 and 12 of the ’689 patent are the only claims remaining for trial.

20. According to the Federal Drug Administration’s (“FDA”) Approved Drug Products with Therapeutic Equivalence Evaluations (the “Orange Book”), the ’689 patent is listed as covering Takeda USA’s Nesina®, Oseni®, and Kazano® products expiring on June 27, 2028.

24. Plaintiff Takeda U.S.A. is the registered holder of approved New Drug Application (“NDA”) Nos. 22-271 (Nesina®), 22-426 (Oseni®), and 203-414 (Kazano®) indicated as adjuncts to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

41. Defendants have stipulated that the commercial manufacture, use, offer for sale, sale or importation of products covered by their respective ANDA submissions prior to the expiration of the ’689 patent will constitute infringement of claims 4 and 12 of the ’689 patent under 35 U.S.C. § 271(a), (b), (c) or (e)(2)(A) if such claims are held valid and enforceable. Therefore, the only issue in dispute in the consolidated action is whether claims 4 and 12 of the ’689 patent are valid.

43. Defendants’ theory based on obviousness-type double patenting is set forth in the reports of their expert Dr. David Rotella, dated June 14, 2019 and August 23, 2019.

44. Defendants’ theory based on 35 U.S.C. § 103 is set forth in the reports of their expert Dr. Dana Ferraris, dated June 14, 2019 and August 23, 2019.

THE ISSUES FOR TRIAL

1. Have Defendants proven by clear and convincing evidence that claims 4 and 12 of the '689 patent are invalid as obvious, pursuant to 35 U.S.C. § 103, or under the doctrine of obviousness-type double patenting?

THE EVIDENCE AT TRIAL

What follows are selected excerpts from the testimony of the witnesses appearing in court at trial:

A. Testimony of David Rotella

Dr. Rotella was qualified as an expert witness in the field of medicinal chemistry and diabetes drug development. (Tr. 15:19-23.) Dr. Rotella recognized Dr. Nichols as an international expert in central nervous system drug discovery. (Tr. 19:1-6.) Dr. Rotella explained that DPP-IV is an enzyme in the human body that inactivates the hormone GLP-1, which stimulates release of insulin from the pancreas. (Tr. 19:20-20:4.) As a result, if one inhibits the action of DPP-IV, one prolongs the life of GLP-1 in the plasma, which allows for continued stimulation for insulin release and lower blood glucose. (Tr. 20:13-17.) Alogliptin is a DPP-IV inhibitor. (Tr. 20:22.) The prior art knew the crystal structure of DPP-IV. (Tr. 22:15-18.) The prior art also knew the location of two binding sites, pockets S1 and S2, which are hydrophobic. (Tr. 23:9-20.) Through computer modeling, one can evaluate the activity of possible DPP-IV inhibitors. (Tr. 24:8-18.)

The '689 patent covers alogliptin, which is used to treat Type 2 diabetes. (Tr. 25:21-26:5.) Claim 4 shows the structure of alogliptin; part of the structure is called the scaffold, and parts are called substituents. (Tr. 27:3-7.) Claim 12 describes the benzoate salt of alogliptin.

(Tr. 27:7-8.) One important characteristic of the alogliptin molecule is an NH_2 group on a substituent that is in the R absolute stereochemistry. (Tr. 28:7-8.)

The Feng or '344 patent was in the prior art and claims DPP-IV inhibitors. (Tr. 29:1-2.) Feng claim 161 discloses a molecule with a structure that has a scaffold that is different from alogliptin, but has the same two substituents present in alogliptin. (Tr. 29:12-15.) Feng claim 162 is a dependent claim that depends on this structure, but it has an error related to the stereochemistry associated with the NH_2 group. (Tr. 29:15-20.) One could change the molecule of the Feng claim 162 compound (hereinafter, "F162") into alogliptin by substituting the scaffold, while keeping the substituents the same. (Tr. 31:15-24.) Scaffold replacement is a common practice in medicinal chemistry. (Tr. 32:1-2.) It was known in the prior art. (Tr. 33:16-18.) One prior art example is the use of scaffold replacement to change celecoxib to rofecoxib. (Tr. 35:1-15.) Another example from after the Priority Date is in a paper in the Journal of Medicinal Chemistry with some authors who are inventors on the '689 patent. (Tr. 36:5-37:12.) In this article, the authors taught the use of scaffold replacement to "go from the Feng patent to the alogliptin patent." (Tr. 37:13-16.)

As to the Kim 1998 reference, Dr. Rotella did not agree that it was an obscure reference that uses a Korean folk remedy. (Tr. 39:7-40:5.) The reference teaches that uracil has activity in an animal model of Type 2 diabetes. (Tr. 41:13-20.) The reference also found that rutin and ascorbic acid have activity, but these will not fit into hydrophobic pockets. (Tr. 43:1-12.) If one substitutes uracil for the scaffold in Feng claim 162, there are four possible structures, and only one ("uracil analogue 1") "matches up in terms of the bond connection between the substituents and the scaffold." (Tr. 45:1-12.)

We replace the scaffold in Feng claim 162 with uracil analogue 1, and then change one hydrogen atom to a methyl group, which is the smallest possible hydrophobic group, and we have alogliptin. (Tr. 46:2-9.) The change to the methyl group is a simple second step that is routine experimentation. (Tr. 46:17-21.)

Dr. Rotella also offered an alternative path to alogliptin. (Tr. 47:6-9.) The compound in Feng claim 162 contains a fluoro-olefin structure which can be replaced with an amide bond, and then you change a nitrogen to a carbon, and you have uracil analogue 1. (Tr. 48:9-22.)

Making a benzoate salt of a compound is a standard practice, commonly used in making an active pharmaceutical ingredient. (Tr. 50:15-25.)

On cross-examination, Dr. Rotella stated that, prior to his involvement in this case, he knew the structure of alogliptin, but that Defendants' counsel had directed him to claim 162 of the Feng patent, as well as the Kim reference. (Tr. 54:16-55:3.)

The central core of alogliptin is a uracil or a pyrimidine-dione, while the central core of Feng claim 162 is a pyrimidinone. (Tr. 58:2-7.) Although some of Dr. Rotella's slides showed a fluorine atom as part of the scaffold, a pyrimidinone scaffold does not have a fluorine atom attached to it; the fluorine is a substituent. (Tr. 58:8-15.) Dr. Rotella did not dispute that F162 would be likely show some effectiveness as a DPP-IV inhibitor. (Tr. 59:9-13.) Dr. Rotella agreed that the Feng patent did not teach or suggest any functional problem with the claim 162 compound, nor suggest that any aspect of the patent's teachings needed modification. (Tr. 59:14-20.) None of the compounds disclosed in the Feng patent has a uracil scaffold. (Tr. 61:11-12.) The Kim reference does not teach inhibition of DPP-IV. (Tr. 61:13-15.) Four prior art references – Wiedeman, the WO '496 patent, the CA '730 patent, and the Mark 2004

patent – disclose many different DPP-IV inhibitors, but none teaches use of a uracil scaffold. (Tr. 62:8-63:6.)

Dr. Rotella stated that he relied on the Böhm reference to say that scaffold hopping was known to the art prior to the critical date. (Tr. 73:16-21.) Dr. Rotella's scaffold replacement theory would be classified as fragment replacement. (Tr. 77:19-23.) The Böhm reference states that fragment replacement requires many noncommercial tools that Dr. Rotella does not know how to use currently, and that the person of ordinary skill in the art ("POSA") prior to the critical date may or may not have known how to use. (Tr. 78:14-24.)

The POSA would have been motivated to modify the Feng claim 162 compound not necessarily to improve it, but to come up with a novel structure. (Tr. 81:9-13.) Dr. Rotella conceded that Wiedeman compound 32 was an exception to Rotella's statement in his opening expert report that all known DPP-IV inhibitors have a positively-charged amine group. (Tr. 83:1-84:1.) Dr. Rotella conceded that in the CA '730 patent, a reference he cited as supporting his belief that a POSA would have preserved the cyanobenzyl substituent group when modifying the Feng claim 162 compound, the four most potent DPP-IV inhibitors disclosed did not have a cyanobenzyl group. (Tr. 88:1-89:12.) Dr. Rotella agreed that, in the specification of the CA '730 patent, the list of exemplary preferred compounds contained none with a cyanobenzyl group. (Tr. 89:16-90:7.) Dr. Rotella agreed that, on page 37 of the CA '249 patent,[1] in a table of 46 exemplary compounds with IC_{50} values, the three compounds containing a cyanobenzyl group, ranked by IC_{50} value, were all in the bottom 6. (Tr. 90:8-91:3.) When asked, "You said that the cyanobenzyl was optimal, didn't you," Dr. Rotella responded, "On a different scaffold,

[1] The transcript states that the question referenced page 47, but this appears to be a typo.

yes." (Tr. 91:20-21.) Dr. Rotella agreed that, of four FDA-approved drugs used for DPP-IV inhibition, only alogliptin has a uracil core or a cyanobenzyl substituent. (Tr. 92:14-93:1.)

As to the fluoro-olefin replacement theory, Dr. Rotella agreed that he knew of no published article in which an amide bond was substituted for a fluoro-olefin. (Tr. 93:25-94:3.) Dr. Rotella agreed that the fluoro-olefin replacement, applied to F162, did not result in a compound with a uracil core, and that an additional step was required, removing a nitrogen atom, to result in a compound with a uracil core. (Tr. 95:5-96:10.)

Dr. Rotella agreed that F162 has one carbonyl group and alogliptin has two. (Tr. 97:13-18.) After the fluoro-olefin replacement of F162, an NH group must be changed to a methyl group. (Tr. 98:6-9.) Dr. Rotella agreed that, at his deposition, with regard to his choosing a methyl group, this exchange occurred:

> Q: Would a bigger alkyl group potentially occupy the S2 site better than methyl?
>
> A: I don't have any information about structure activity relationships in that case. However, adding a methyl group simply gets you, as indicated, from compound 1 to alogliptin.

(Tr. 104:2-13.) Dr. Rotella stated that one would start with a methyl group because it is the smallest possible hydrophobic substituent. (Tr. 104:18-20.) Dr. Rotella agreed that a POSA would start with F162 and that "the motivation for the skilled artisan to make changes to that compound would be to create potentially novel compounds that inhibit DPP-IV." (Tr. 105:1-5.) Dr. Rotella stated that it would surprise him to learn that, at his deposition, he stated that the simplest way to get a novel compound that inhibits DPP-IV from F162 would be to switch the scaffold, but he accepted that he said that. (Tr. 105:18-23.) He agreed that it was simpler to change the scaffold than to change any one of the substituents. (Tr. 105:24-106:5.) As of the

Priority Date, there were no publications which disclosed the DPP molecule with a non-peptidic DPP-IV inhibitor. (Tr. 110:9-13.)

B. Testimony of Dana Ferraris

Dr. Ferraris was qualified as an expert in medicinal chemistry, including the design and development of drugs. (Tr. 132:19-23.) A POSA, as of the critical date, would have selected DCAX as a lead compound in research to develop a DPP-IV inhibitor. (Tr. 139:25-140:5.) A POSA would have selected DCAX for these reasons: 1) it is non-peptidic; 2) it was identified by two major pharmaceutical companies; 3) it was very potent against the enzyme; and 4) it has cyano- and amino- substituent groups, which were known to be important for DPP-IV binding. (Tr. 141:12-24.) Research prior to the Priority Date on peptide-based inhibitors had shown chemical stability issues. (Tr. 142:9-24.) That was stated in the Wiedeman and Lambeir references. (Tr. 143:3-23; 144:3-145:5.) The Wiedeman reference has a discussion of research on non-peptidic inhibitors in four chemical groups. (Tr. 146:10-147:3.) One group, the xanthines, was reported to have members that were active in animal models of diabetes, to have some that were very potent, and that two major pharmaceutical companies, Novo Nordisk and Boehringer Ingelheim, independently came up with this series of compounds. (Tr. 148:8-20; 149:3-19.) A POSA would have looked at the publications cited by Wiedeman to learn more about the xanthines, the Novo Nordisk WO ’496 patent and Boehringer Ingelheim’s German equivalent of the CA ’730 patent. (Tr. 149:20-150:19.) The Novo Nordisk patent points to DCAX as its first example, and a POSA would think that the first compound was a lead compound. (Tr. 151:20-152:8.) The CA ’730 patent lists IC_{50} potency data for a group of compounds, and DCAX has a value of 10, which is very potent, and some listed compounds

have values of 2 and 6. (Tr. 154:3-15.) There is a reason to choose DCAX as a lead compound over the other listed high potency compounds: only DCAX has a cyanobenzyl group, and the other four have a methylbutyl group, and the cyanobenzyl group was well-known to be prevalent in DPP-IV inhibitors. (Tr. 155:4-12.) The Wiedeman reference shows how many of the DPP-IV inhibitors have both cyano and amino groups. (Tr. 156:7-22.) Wiedeman reports that the presence of the cyano group has been extensively investigated, and that compounds with that group had been found to be potent, stable, competitive, and slow-binding DPP-IV inhibitors. (Tr. 157:3-8.) The CA '730 patent also shows that the cyano group has a significant effect on potency. (Tr. 158:7-9.) As shown in Wiedeman, virtually all DPP-IV inhibitors also have an amino group. (Tr. 158:15-18.)

After a POSA selects a lead compound, the next step is to optimize that lead, possibly to improve its potency, solubility, permeability, or metabolic stability. (Tr. 160:12-25.) A POSA would have three major reasons to optimize DCAX: 1) to find a patentable and marketable drug; 2) to improve pharmaceutical properties; and 3) questions about the effect of the scaffold of the molecule. (Tr. 162:1-16.) A POSA might want to decrease the ring size from a two-ring system to a one-ring system to improve solubility. (Tr. 163:9-24.)

The large number of references to scaffold hopping cited in Böhm supports the view that scaffold hopping was a common technique prior to the Priority Date. (Tr. 166:4-9.) Böhm teaches that a POSA might want to change the scaffold to increase solubility, or to produce novelty for patentability. (Tr. 167:1-6.) Changing the scaffold so as to reduce the number of rings from two to one could improve solubility, step away from the intellectual property of xanthine-based compounds, and, if the new scaffold is close to xanthine, the new compound

would be potent. (Tr. 168:12-19.) A change to a uracil scaffold yields those results. (Tr. 169:5-14.) Because DCAX is a very potent compound, a POSA wouldn't want to change the scaffold too much. (Tr. 170:22-171:1.) Also, a POSA would want to substitute another naturally-occurring nitrogenous base for the xanthine because they are readily available, their synthesis is well-established, they are naturally-occurring substances and so less toxic, and they appear in many drugs. (Tr. 171:5-25.) Changing the scaffold from xanthine to uracil is a trivial task and would probably take one person a week in the lab. (Tr. 172:2-7.) The '051 patent and the Davies paper use these nitrogenous bases interchangeably. (Tr. 172:14-16.)

The Novo Nordisk patent discloses the R stereoisomer of DCAX, so the POSA would favor the R isomer. (Tr. 177:10-13.) R-DCAX has the same stereochemistry as alogliptin. (Tr. 177:21-178:2.) It was a routine practice at the time to make and test different salts of an active ingredient for pharmaceutic reasons, using a salt panel, a series of FDA-approved salts, of which benzoate is one. (Tr. 179:21-180:25.) Creating salts of alogliptin is very easy. (Tr. 181:20-21.)

On cross-examination, Dr. Ferraris said that he did not find the WO '496 patent and the CA '730 patent on his own; these were given to him by counsel. (Tr. 188:12-21.) He was asked by counsel to see whether a POSA would modify DCAX in a logical and straightforward way, and what the product would be. (Tr. 188:25-189:4.) Counsel asked him to assume that a POSA would start with DCAX. (Tr. 189:8-10.) Dr. Ferraris agreed that, at his deposition, he stated that he was tasked with finding the path of least resistance between DCAX and alogliptin. (Tr. 189:21-190:17.) As of March 2004, there wasn't a crystal structure of the DPP-IV enzyme with a non-peptidic inhibitor. (Tr. 191:1-4.) Xanthines were not the only kinds of compounds

being studied as DPP-IV inhibitors in March of 2004. (Tr. 191:8-11.) Dr. Ferraris agreed that the Wiedeman reference talks a lot about research on peptidic inhibitors, and that a number of companies in 2003-2004 were studying them. (Tr. 191:21-192:13.)

Dr. Ferraris himself was studying peptidic DPP-IV inhibitors in 2000, and he published a paper in 2004 about his work exclusively on peptidic inhibitors, which does not mention xanthine or uracil compounds. (Tr. 193:6-194:1.) Dr. Ferraris agreed that the goal of his work was to pick inhibitor candidates to develop into a therapeutic product. (Tr. 194:15-19.) Dr. Ferraris was lead author on a 2007 review article about his work, and the article did not mention xanthine or uracil compounds. (Tr. 194:10-195:3.) Dr. Ferraris did not recall ever telling a boss that they should stop the work on peptidic inhibitors and research only non-peptidic inhibitors, or saying that the only obvious choice was xanthine compounds. (Tr. 195:23-196:5.) The Wiedeman reference mentions research on xanthine-based non-peptidic inhibitors, but also aminomethylisoquinolones, aminomethylisoquinoline, aminolactams, and sulfonyltriazoles. (Tr. 196:11-197:1.) The most potent compound mentioned in any reference Dr. Ferraris cited is sulfonyltriazole, in the Wiedeman reference. (Tr. 198:15-199:13.) Given the potency of that compound, a POSA in March of 2004 would consider it as a potential lead compound, but Dr. Ferraris believed it might have some chemical stability issues. (Tr. 206:16-23.) Dr. Ferraris did not know of any reference that teaches stability issues with that compound. (Tr. 207:2-4.) Dr. Ferraris agreed that a POSA would at least study this potent compound to figure out about stability problems and whether such problems could be optimized. (Tr. 207:25-208:5.) Dr. Ferraris had done no reading beyond the Wiedeman reference about the non-xanthine-based non-peptidic inhibitors. (Tr. 208:7-20.)

Dr. Ferraris agreed that the WO ’496 patent discloses 103 xanthine compounds. (Tr. 209:16-21.) He did not know of any reference that taught that the first example given has to be the primary candidate. (Tr. 211:7-20.) The CA ’730 patent discloses more than 800 xanthine compounds. (Tr. 212:23-25.) DCAX is the 121st example under Example 1. (Tr. 213:13-19.) The CA ’730 patent lists 38 preferred compounds, but DCAX is not on that list. (Tr. 214:4-9.) Dr. Ferraris agreed that the Mark 2004 patent lists 30 “most particularly preferred” compounds and DCAX is not on that list. (Tr. 218:1-6.) None of the compounds on that list has a cyanobenzyl group. (Tr. 219:15-22.) In the CA ’730 patent, none of the 38 preferred compounds has a cyanobenzyl group. (Tr. 219:23-220:4.) Looking at the CA ’730 patent and the Mark 2004 patent together, there are 38 xanthine compounds (“the 38X Compounds”) with IC_{50} values lower than DCAX. (Tr. 220:5-9.) These two patents list 8 compounds in common, of which DCAX is one. (Tr. 220:21-221:9.) Wiedeman Figure 2 depicts peptidic inhibitors, none of which has a cyanobenzyl group. (Tr. 222:19-223:14.) Boehringer did not pick DCAX to develop. (Tr. 224:4-6.) One of the 38X Compounds is linagliptin, a xanthine compound, without a cyanobenzyl group, and Boehringer developed this and markets it now under the name Tradjenta. (Tr. 225:4-22.) A Boehringer scientist could have put a cyanobenzyl group on linagliptin. (Tr. 226:5-8.)

Dr. Ferraris agreed with this statement: “the goal of a medicinal chemist is to take a lead compound, make minor modifications to it, retain as much as you need to retain to get to the final drug, which is an iterative process.” (Tr. 229:6-10.) Novo and Boehringer experimented with removing substituent groups from DCAX. (Tr. 230:4-16.) The only reason that a POSA would have been motivated to replace the xanthine scaffold of DCAX with a uracil was because

DCAX was patented. (Tr. 230:17-22.) Dr. Ferraris did not do an analysis of the patent landscape around uracil compounds. (Tr. 232:1-4.)

The ‘051 patent teaches not only that one can replace a xanthine core with a uracil, but also with thymine, cytosine, guanine, adenine, and hypoxanthine. (Tr. 234:7-21.) Neither the ‘476 nor the ‘051 patents, nor the Davies reference, has an example of replacement of a xanthine core with a uracil core. (Tr. 236:23-237:22.) In the 2004 and 2007 papers on DPP-IV inhibitors that Dr. Ferraris published, he did not use a scaffold hopping technique like the one in his theory in this case. (Tr. 237:24-238:8.)

A POSA who wanted to build a molecule with a uracil core and cyanobenzyl and aminopiperidinyl substituents would need to choose from several different places on the core where the substituents could be attached. (Tr. 240:12-18.) There are three other possible arrangements in addition to that of alogliptin. (Tr. 240:19-241:23.) Even if the POSA chose the substituent arrangement of alogliptin, the resulting compound would not yet be alogliptin, which has a methylated uracil. (Tr. 241:24-242:5.)

On redirect examination, Dr. Ferraris said that while Wiedeman Figure 2 contains no compounds with cyanobenzyl substituents, at least three compounds have cyano groups. (Tr. 248:2-17.) Multi-ring compound structures like DCAX often are insoluble, and one common strategy for dealing with that is to change the multi-ring structure to a single ring. (Tr. 261:7-17.)

C. Testimony of David Nichols

Dr. Nichols was qualified as an expert in the fields of medicinal chemistry, pharmacology, and drug development. (Tr. 287:17-21.) Dr. Nichols said that he disagreed

with the opinions of Drs. Rotella and Ferraris. (Tr. 288:9-12.) The alogliptin molecule has a uracil core with three substituent groups attached: a methyl, a cyanobenzyl, and an aminopiperdinyl group, specifically the R stereochemistry. (Tr. 290:10-291:1.) Dr. Nichols had done an analysis of the state of the relevant art as of March of 2004. (Tr. 295:12-15.)

Dr. Nichols saw nothing in the ’344 patent that would teach a POSA about problems with any specific compound disclosed in that patent. (Tr. 299:1-4.) There are an almost infinite number of ways a POSA could change F162. (Tr. 299:513-19.) The fluorine in the alogliptin molecule is a substituent attached to the scaffold and not a part of the scaffold. (Tr. 305:4-11.) There are quite a few differences between F162 and alogliptin, and these differences have biological significance. (Tr. 306:2-9.)

Dr. Rotella’s statements about scaffold hopping are misleading. (Tr. 309:14-15.) One doesn’t just cut out the xanthine and put in a uracil – that’s not how it works; rather, it’s an evolutionary process. (Tr. 309:9-14.) One changes one component, and then sees whether activity has increased or decreased. (Tr. 310:4-19.) If one were to swap the pyrimidone scaffold for a uracil, a POSA would not be able to predict the properties of the resulting compound. (Tr. 310:23-311:4.) As of 2004, the art knew of crystal structures only for the unbound enzyme with no ligand and for the enzyme bound to a peptidic ligand. (Tr. 311:14-25.) If one were to study non-peptide inhibitors, you need a crystal structure of a non-peptide inhibitor bound to the enzyme, which the art did not have. (Tr. 312: 11-19.) It would be very difficult, if not impossible, without very advanced computational tools to imagine what the active site would look like with a non-peptide inhibitor bound. (Tr. 312:20-22.) The peptidic inhibitors and non-peptidic inhibitors are very different. (Tr. 313:3-14.) The art in 2004 did

not know how non-peptide structures would bind to the enzyme active site. (Tr. 314:1-9.) Böhm states that scaffold hopping requires the availability of a template, the three-dimensional structure of the molecule you want to do the scaffold hop on. (Tr. 314:10-21.) Dr. Rotella misrepresented Figure 1; scaffold hopping just means that there are two different structures that have the same biological activity, not that one evolved from the other. (Tr. 315:4-15.) Dr. Rotella did not understand what scaffold hopping was as of the Priority Date. (Tr. 315:25-316:4.)

Dr. Nichols said that he had done research on dopamine and apomorphine, and that Böhm gives that pair as an example of scaffold hopping, but they were discovered independently by completely divergent thinking. (Tr. 316:6-317:25.) What Böhm means with the examples of scaffold hopping is that the two molecules have the same biological activity, not that one was derived from the other by a change of scaffold. (Tr. 317:25-318:6.) In the conclusion, Böhm states that serendipity played a large role in many of the discoveries; they weren't an evolution. (Tr. 319:1-11.) A ligand may bind to a target in different ways and, if you don't know how it binds, it's difficult to develop a specific scaffold-hopping approach. (Tr. 320:17-21.)

Böhm Table 1 shows four computational techniques to perform scaffold hopping, giving the pros and cons of each. (Tr. 321:2-19.) Shape matching has a "con" listed, that it requires three-dimensional information about the binding of the inhibitor to the enzyme, which was not known for non-peptidic inhibitors as of the Priority Date. (Tr. 322:3-11.) Pharmacore searching again requires knowledge about the bioactive conformation and alignment; also, Böhm notes that there are many company-specific non-commercial tools, which would not have been available to the POSA. (Tr. 322:13-25.) The skill set that would have been required to do

"plug and play" scaffold hopping would not have been available to the POSA in 2004; specialists in computational chemistry had those skills. (Tr. 323:1-13.)

The Kim reference does not even mention DPP-IV inhibitors. (Tr. 327:2-6.) A POSA in March of 2004 working on DPP-IV inhibitors would not have found the Kim reference; Dr. Nichols was unable to find it in PubMed, the major database most scientists would use. (Tr. 327:7-17.) The Kim reference discloses research which found that uracil and vitamin C both had the ability to lower blood sugar. (Tr. 329:21-24.) The Kim reference would not have motivated a POSA to replace the scaffold of F162 with uracil. (Tr. 331:4-8.)

To get from F162 to alogliptin, a POSA would need to replace the pyrimidinone core with uracil, get rid of the fluorine atom, select from three possibilities the proper position to attach the cyanobenzyl and aminopiperidinyl groups to the uracil, add a methyl group, and choose the stereochemistry for the amino group. (Tr. 331:15-334:20.)

As for Dr. Rotella's alternative fluoro-olefin replacement theory, he argues that an amide is a bioisostere (having similar biological activity) for the fluoro-olefin unit on F162. (Tr. 335:6-16.) Neither the '344 patent nor any other prior art reference taught a reason to get rid of a fluoro-olefin unit. (Tr. 335:17-23.) Dr. Nichols did not know of any prior art references that taught replacing a fluoro-olefin with an amide, though there are ones that teach the reverse, as Dr. Rotella said, but one would not have known whether it would work in the opposite direction. (Tr. 335:24-336:7.) If one did that replacement, there are two possible orientations for doing the replacement, and the proper orientation is not the one Dr. Rotella chose. (Tr. 336:8-25.) If, however, one chose the orientation as Dr. Rotella did, there is an extra nitrogen atom that must be replaced with a carbon atom. (Tr. 338:10-16.) Then an n-methyl group must be added, then

one has to choose the R stereochemistry in the 3-amino group. (Tr. 339:1-17.)

As to Dr. Ferraris' obviousness analysis, both the WO '496 and CA '730 patents are exclusively directed to xanthine-based compounds. (Tr. 340:12-20.) Dr. Nichols agreed with Dr. Ferraris that the peptidic inhibitors were known to have stability problems. (Tr. 341:13-22.) Nonetheless, a POSA would not have completely ignored peptidic compounds, because there might be ways around that. (Tr. 341:23-342:1.) Compound 32 in Wiedeman, the Eisai compound, is not a xanthine, and there is not a more potent inhibitor disclosed in the prior art; this would have been very attractive to a POSA seeking to develop a DPP-IV inhibitor. (Tr. 342:7-344:23.) Dr. Nichols disagreed with Dr. Ferraris that compound 32 would have stability problems. (Tr. 345:3-6.) First of all, compound 32 is a patented compound, and no company would spend large amounts of money to develop an unstable compound. (Tr. 345:8-11.) Also, Dr. Ferraris said that compound 32 resembled carbonyldiimidazole, but compound 32 is not an imidazole; it is a carbamoyl, which are less reactive. (Tr. 345:12-18.)

Wiedeman does not disclose DCAX. (Tr. 345:21-23.) Nor would a POSA have focused only on xanthines. (Tr. 345:24-346:2.) Dr. Nichols disagreed that the fact that DCAX is listed first in the WO '496 patent would be significant to a POSA; he has never seen any relationship between the order of presentation of examples and their desirability. (Tr. 346:14-20.) DCAX is one of 880 compounds named in the CA '730 patent. (Tr. 347:17-24.) It was not one of the 38 compounds listed as preferred. (Tr. 348:7-349:2.) The second most potent preferred compound in the CA '730 patent was described by Wiedeman as a potent xanthine. (Tr. 350:1-25.)

Of the five most potent compounds reported with potency data in the CA '730 patent,

DCAX is the least potent, and has a cyanobenzyl attached at the 7 position and an aminopiperidinyl at the 8 position. (Tr. 352:1-12.) The four more potent compounds have a methyl-butenyl at the 7 position. (Tr. 352:16-24.) Of the 38 preferred compounds, none had a cyanobenzyl group. (Tr. 353:6-9.) Of the 333 tested for potency, ten had cyanobenzyl. (Tr. 353:12-13.) Of the preferred compounds, 28 out of 38 had methyl-butenyl groups. (Tr. 353:14-16.) Based on the information in the CA '730 patent, a POSA would not have chosen a compound with a cyanobenzyl group as the lead compound. (Tr. 353:20-24.)

The Mark 2004 reference deals only with xanthines, and 46 compounds were tested for potency, with DCAX not among them. (Tr. 354:14-355:3.) Of the 46 tested compounds, three have a cyanobenzyl group, ranking 41st, 43rd, and 45th least potent. (Tr. 355:9-20.) DCAX is not among the 30 most particularly preferred compounds, nor are any compounds with a cyanobenzyl group. (Tr. 356:1-9.) Neither the Mark 2004 reference nor the CA '730 patent discloses any problems with the tested compounds with higher potency than DCAX, such that a POSA would have been motivated to ignore them. (Tr. 356:13-22.)

Wiedeman Figure 2 discloses only peptidic molecules, and none have a cyanobenzyl group. (Tr. 357:4-15.) Dr. Nichols has seen no evidence that a POSA in 2004 would have selected DCAX as a lead compound. (Tr. 357:23-358:2.) The "near explanation" for Dr. Ferraris' theory of the path from DCAX to alogliptin, as to replacing the core with a uracil, would be scaffold hopping. (Tr. 359:7-11.) Dr. Ferraris relied on three substitution references for the proposition that a uracil is functionally equivalent to a xanthine but none of them teach anything about DPP-IV inhibitors, scaffold hopping, uracil in DPP-IV inhibitors, or whether uracil and xanthine are interchangeable. (Tr. 362:15-20.) Dr. Nichols has seen nothing in the

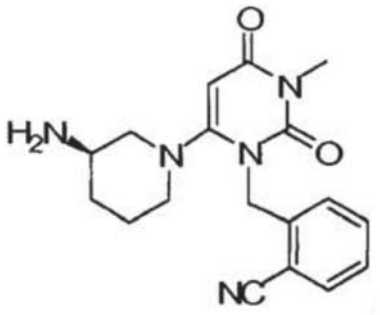
prior art that suggests that xanthine and uracil are interchangeable as scaffolds. (Tr. 362:21-23.) The fact that a methyl group is tolerated by the DPP-IV enzyme was unknown to the POSA in 2004. (Tr. 364:13-16.)

On cross-examination, Dr. Nichols said that the Böhm reference applies the term, "scaffold hopping," to examples which Dr. Nichols believed did not represent scaffold hopping; it is not a simple replacement of the scaffold. (Tr. 391:11-21.) Dr. Nichols had not heard about scaffold hopping until he read Dr. Rotella's expert report. (Tr. 393:12-19.) Dr. Nichols did not review any of Böhm's references. (Tr. 394:16-23.) The Kanstrup reference teaches potent DPP-IV inhibitors with both cyanobenzyl and aminopiperidinyl substituents. (Tr. 400:406.) Dr. Nichols agreed that the basic requirement for identifying a lead compound is that it has some degree of the activity one is looking for. (Tr. 406:19-21.) Ease of modification would also be a consideration. (Tr. 408:2-9.) Wiedeman teaches choosing xanthine-based compounds as non-peptidic inhibitors. (Tr. 409:4-6.) One cannot convert a molecule with a xanthine scaffold directly into a molecule with a uracil scaffold; one has to do a total synthesis of the molecule. (Tr. 413:15-21.)

DISCUSSION

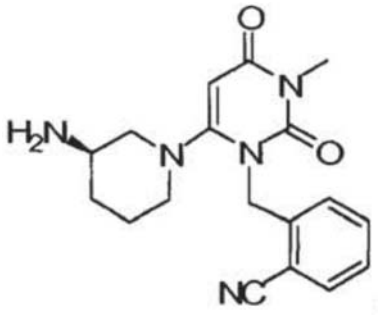
Claims 4 and 12 of the ’689 patent are at issue:

4. A compound of the formula



or pharmaceutically acceptable salts thereof.

12. A compound of the formula



wherein the compound is present as a benzoate salt.

The ’689 patent descends from provisional application No. 60/553,571, filed on March 15, 2004 (the “Priority Date.”)

The Federal Circuit has summarized the fundamental principles of the law of obviousness as follows:

> Under § 103, a patent may not issue “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103 (2006). Obviousness is a question of law based on underlying factual

> determinations, including: (1) the scope and content of prior art; (2) differences between prior art and claims; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham v. John Deere Co*., 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966). A party asserting that a patent is obvious must demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.

Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186, 1193 (Fed. Cir. 2014).

The Federal Circuit has summarized the fundamental principles of the law of obviousness-type double patenting as follows:

> Nonstatutory double patenting, however, is a judicially-created doctrine, which prohibits an inventor from obtaining a second patent for claims that are not patentably distinct from the claims of the first patent. It prevents the extension of the term of a patent, even where an express statutory basis for the rejection is missing, by prohibiting the issuance of the claims in a second patent not patentably distinct from the claims of the first patent.
>
> The obviousness-type double patenting analysis involves two steps: First, the court construes the claims in the earlier patent and the claims in the later patent and determines the differences. Second, the court determines whether those differences render the claims patentably distinct. The second part of this analysis is analogous to the obviousness inquiry under 35 U.S.C. § 103 in the sense that if an earlier claim renders obvious or anticipates a later claim, the later claim is not patentably distinct and is thus invalid for obviousness-type double patenting. In chemical cases, the double patenting inquiry is not whether a person of ordinary skill in the art would select the earlier compound as a lead compound, but rather whether the later compound would have been an obvious or anticipated modification of the earlier compound. Unlike in an obviousness analysis, the underlying patent in the double patenting analysis need not be prior art to the later claim.

UCB, Inc. v. Accord Healthcare, Inc., 890 F.3d 1313, 1323 (Fed. Cir. 2018) (citations omitted.)

Furthermore:

> Unless the earlier claim anticipates the later claim under § 102, the question whether the two claimed compounds are 'patentably distinct' implicates the question of obviousness under § 103, which in the chemical context requires identifying some reason that would have led a chemist to modify the earlier

compound to make the later compound with a reasonable expectation of success. Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1297 (Fed. Cir. 2012) (citation omitted.) "Whether a person of ordinary skill would have been motivated to modify the teachings of a reference is a question of fact." Amerigen Pharm. Ltd. v. UCB Pharma GmbH, 913 F.3d 1076, 1086 (Fed. Cir. 2019).

Defendants Torrent and Indoco coordinated their defense. In the post-trial briefing, Torrent presented Defendants' case on obviousness-type double patenting, and Indoco presented Defendants' case on obviousness.

The law of statutory obviousness and the law of obviousness-type double patenting have in common, *inter alia*, the requirement that the POSA have a reasonable expectation of success in modifying the prior art. Defendants' three invalidity theories in this case, therefore, all must meet this requirement. As will be seen, two of Defendants' three theories rely heavily on a chemistry technique termed scaffold hopping or scaffold replacement. At the outset, the Court notes that the evidence at trial supports the inference that, in the art of pharmaceutical development, it is difficult to accurately predict the biological effects of the modification of molecules, even when the modification entails a small change. Defendants relied on the teachings of the Böhm reference on scaffold hopping, JTX-0009, and both parties treated that reference as authoritative.[2] As Takeda notes, the introduction in Böhm states:

> There are numerous cases demonstrating that very small changes can have dramatic effects on the molecular properties, and thus a pharmacologist might judge from the function of a compound and will regard an agonist as being

[2] While Dr. Nichols spoke of some points of disagreement with the Böhm reference, his disagreement was more with Defendants' interpretation of Böhm than with the statements about scaffold hopping that Böhm made. Plaintiffs' post-trial brief contends that the Böhm reference "generally describes the state of the art at the time of the invention." (Takeda PTB at 21 n.9.)

> different from an antagonist, even if it the compounds differ by one minor substituent only.

(JTX-0009 at 1.) According to Böhm, very small changes – such as a change in one minor substituent – can have dramatic effects on molecular and pharmacological properties. At trial, Dr. Rotella was asked about this statement in Böhm, and he agreed with it. (Tr. 74:10-19.) The Court thus begins the discussion by making a finding of fact that, in the relevant art of pharmaceutical development, very small changes in molecular structure can have dramatic effects on the properties of the molecule. This finding is quite relevant to the assessment of the expectation of success from modifying molecules. "[P]redictability is a vital consideration in the obviousness analysis." Otsuka, 678 F.3d at 1298.

This finding of fact is relevant to all three of Defendants' theories. Although the isosteric replacement theory does not involve scaffold replacement, it does involve changing the molecular structure of a compound. There is no evidence of record that isosteric replacement is an area in which changes in molecular structure have more predictable effects on molecular properties than is the case with scaffold replacement.

Two of Defendants' three theories involve the use of the technique of scaffold replacement. The Böhm reference states:

> Here, we focus on a concept that is vividly, if somewhat casually, described by the term ''scaffold hopping'' (Box 1). This approach requires the availability of a template – a chemical structure displaying the desired biological activity, and it is based on the assumption that the same biological activity can be exerted by other compounds that maintain some essential features of the template but are structurally different otherwise.

(JTX-0009 at 1.) With regard to the template, Dr. Nichols explained: "That means the structure, the three-dimensional structure of the molecule you want to do the scaffold hop on." (Tr.

314:19-21.) Böhm states that the template displays the desired biological activity, which, in this case, would be a non-peptidic compound binding to the DPP-IV enzyme. No expert disputed this statement in Böhm. The Court makes the factual determination that the prior art believed that success in scaffold hopping required the availability of a template of the desired biological activity.

Dr. Ferraris agreed that, as of the Priority Date, a crystal structure of the DPP-IV enzyme bound to a non-peptidic inhibitor was unknown in the art. (Tr. 191:1-4.) Dr. Nichols agreed. (Tr. 311:23-25; 312:16-19.) Dr. Rotella also agreed. (Tr. 110:9-13.) This is a point on which the three experts agreed, and this Court finds that it is undisputed that, as of the Priority Date, the art did not have a crystal structure of the DPP-IV enzyme bound to a non-peptidic inhibitor. Dr. Nichols also testified that, to study non-peptide inhibitors, you needed this crystal structure of a non-peptide inhibitor bound to the enzyme. (Tr. 312: 11-19.) Dr. Nichols also stated that the art in 2004 did not know how non-peptide structures would bind to the enzyme active site. (Tr. 314:1-9.) There was no contrary testimony about the need for this crystal structure, or the state of the prior art. Neither Dr. Rotella nor Dr. Ferraris testified that he had found and examined a template, within the meaning of the Böhm reference, and considered essential features of the template in the analysis. There is no evidence of record that the prior art possessed either a template, within the meaning of the Böhm reference – a chemical structure displaying the desired biological activity –, or a crystal structure of a non-peptide inhibitor bound to the DPP-IV enzyme. This Court determines, as a factual matter, that, as of the Priority Date, the relevant art did not have available the structural information needed to perform scaffold hopping on a non-peptidic DPP-IV inhibitor with a reasonable expectation of success.

The parties began the presentation of their cases by disputing the qualifications of a person of ordinary skill in the relevant art ("POSA.") This Court need not reach this dispute because it has no effect on the outcome: even if Defendants are correct in this, they still fail to prove invalidity by clear and convincing evidence.

A. Patent invalidity: obviousness-type double patenting

Torrent argues that claims 4 and 12 are invalid, under the doctrine of obviousness-type double patenting, because they are not patentably distinct from F162, the compound disclosed in claim 162 of the '344 patent. Thus, the obviousness-type double patenting inquiry in this case focuses on the question of whether the compounds in claims 4 and 12 are patentably distinct from F162. Under Otsuka, Defendants must identify some reason that would have led a chemist to modify F162 to make the compounds of claims 4 and 12 with a reasonable expectation of success.

Torrent begins by arguing that there is an obvious mistake in claim 162, and that the Court should adopt its proposed construction of that claim. The Court need not resolve this issue to rule on this case. Torrent has failed to show, by clear and convincing evidence, that claims 4 and 12 are not patentably distinct from claim 162 under *any* construction. Torrent proposes that claim 162 of the '344 patent should be construed to include the R stereochemistry for the aminopiperidinyl substituent. This Court will take this as true solely for the purpose of evaluating Torrent's obviousness-type double patenting case. The practical impact of this is that this Court will evaluate Torrent's argument without considering the question of whether it is obvious to modify F162 to have R stereochemistry for the aminopiperidinyl substituent.

1. Torrent's first ODP theory

Torrent proposes two theories, which it calls alternative pathways. Torrent summarizes the first theory as follows:

> Torrent's alternative pathway 1 relies upon 2 steps: (1) replacing the pyrimidinone scaffold of claim 162 with the uracil scaffold while retaining necessary substituents and eliminating unnecessary substituents on the scaffold as set forth in the Böhm reference; and then (2) after the scaffold replacement (which then converts it to a uracil analogue), engaging in routine optimization to ensure that the uracil analogue has the right orientation followed by tweaking one substituent to optimize its binding ability on the DPP-IV enzyme.

(Torrent PTB at 13.) As to the first step, the question is whether it would have been obvious to modify F162 to replace the pyrimidinone (xanthine) scaffold with a uracil scaffold. Torrent relies on two propositions to make its case in support: 1) scaffold replacement was a technique well-known in the prior art; and 2) the Kim reference provides motivation to a POSA to replace the pyrimidinone (xanthine) scaffold of F162 with a uracil scaffold, while leaving the substituents intact. This Court considers the second proposition first.

Torrent states, correctly: "The main point of dispute between the parties concerns the motivation of a POSA to modify only the scaffold of the claim 162 compound to replace it with [the] uracil scaffold based on the disclosures regarding uracil in Kim." (Torrent PTB at 22.)

The Kim reference is a 1998 publication in the Journal of Applied Pharmacology with the title, "Anti-diabetic Activity of Constituents of Lycii Fructus;" Kim is the first of several authors. (JTX-0016.) The paper describes a research study on compounds derived from a plant, *lycii fructus*. (Id. at 1.) In short, the authors performed a chemical analysis on plant material and found the substances uracil, rutin, and betaine. (Id. at 2, 3.) The authors administered uracil,

rutin, and betaine, as well as ascorbic acid and Daonil,[3] to rats with induced diabetes, and measured the effect on blood glucose in the rats. (Id. at 4.) The study reports blood glucose inhibition rates of 18.3% for the 45 mg/kg oral dose of uracil and 18.1% for the 45 mg/kg oral dose of ascorbic acid. (Id.) The authors concluded that uracil, rutin, and ascorbic acid demonstrated "significant anti-diabetic effects, suggesting their potential as new diabetes treatment." (Id. at 6.)

The first heading for the section of Torrent's post-trial brief that deals with the motivating impact of the Kim reference appears on page 22: "The Kim Reference Provides Motivation To A POSA To Utilize A Uracil Scaffold As A Replacement Of The Of [*sic*] Claim 162." Torrent then presents five propositions regarding the content of the prior art; none concern the Kim reference, or the use of uracil. One proposition asserts that uracil is a "part" of xanthine, citing Dr. Rotella's testimony that, if you remove three atoms from the xanthine scaffold, you have a uracil scaffold. (Tr. 43:20-25.) Next comes a subheading: "The Kim Reference Would Have Motivated A POSA To Replace The Scaffold Of Claim 162 From A Pyrimidinone Core To A Pyrimidine-Dione Core (While Leaving The Substituents Intact)." (Torrent PTB at 22.) It is after this subheading that Torrent asserts, as quoted above, the main point of dispute between the parties.

Torrent's post-trial brief next makes a short argument that Takeda is wrong on the relevant law, and then makes the uncontroversial assertion that motivation can be demonstrated in a variety of ways. (Torrent PTB at 23.) Torrent then cites and quotes selectively from the

[3] Dr. Nichols stated that Daonil is a known drug for treating diabetes and is not a DPP-IV inhibitor. (Tr. 329:17, 331:2-3.) The Kim reference does not mention DPP-IV inhibition. (Tr. 61:25-62:2.)

Federal Circuit's decision in Altana Pharma AG v. Teva Pharm. USA, Inc., here presented in its original form and context:

> Obviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound. *Eisai*, 533 F.3d at 1357. The requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *Id.* (citing *Aventis Pharma Deutschland GmbH v. Lupin, Ltd*., 499 F.3d 1293, 1301 (Fed. Cir. 2007)). Instead, "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.*

Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1007 (Fed. Cir. 2009). There are a number of things to say about this citation. First, and most significantly, it appears to have nothing to do with the Kim reference, or Torrent's argument about the Kim reference. Does Torrent contend that the Kim reference teaches a structural similarity between F162 and the compound that would exist if one replaced the xanthine scaffold of F162 with a uracil scaffold, while keeping the substituents intact (hereinafter, "F162u")? What argument is this supporting?

Next, after a district court citation, Torrent cites and quotes from the Federal Circuit's decision in In re Mayne, here presented in its original form and context:

> A comparison of Phe-Pro-Ile and Leu-Pro-Leu in the prior art with the claimed Phe-Pro-Leu suggests structural similarity. Structural relationships often provide the requisite motivation to modify known compounds to obtain new compounds. *In re Deuel*, 51 F.3d at 1558. In fact, Leu is an isomer of Ile - an identical chemical formula with differences only in the chemical bonding of the atoms. The side chains, also known as R-groups, of Leu and Ile have the same number of hydrogen and carbon atoms. Both are nonpolar, hydrophobic amino acids. The structure of Leu and Ile alone suggest their functional equivalency.
>
> Moreover, two of the activation sequences revealed by Light have either an Ile or a Leu at the third position. Light, too, suggests substitution of Leu for Ile at that third position of the activation sequence. In view of Light and the similarities between Leu and Ile, Phe-Pro-Leu-(Asp)4-Lys-Y is an obvious functional

> equivalent to enterokinase recognition sequences disclosed in the prior art. This court detects no error in the PTO's prima facie obviousness case.

In re Mayne, 104 F.3d 1339, 1343 (Fed. Cir. 1997). Again, there are a number of things to say about this citation. Again, it appears to have nothing to do with the Kim reference, or Torrent's argument about the Kim reference. Nor has Torrent explained its application to this case. The cited portion of Mayne appears to deal with the PTO's prima facie obviousness case, which is not at issue here. Again, what argument does this support?

The next subsection carries this subheading: "Claim 162 Of The Feng Patent And Claims 4 And 12 of The '689 Patent Exhibit Structural Similarity." (Torrent PTB at 24.) In the paragraph that follows, Torrent asserts that F162 and the compounds of claims 4 and 12 of the'689 patent have in common the cyanobenzyl and aminopiperidinyl substituent groups, the R stereochemistry (if one corrects the alleged mistake in claim 162), and scaffolds with six-member pyrimidine structures. Torrent concludes: "On this basis *alone*, the case law supports motivation of a POSA to modify claim 162." (Torrent PTB at 24.) This assertion is offered without any analysis or argument beyond what has been mentioned. The brief then cites to three paragraphs in its proposed conclusions of law – but there is no citation to any evidence.

There are a number of big problems here. First, Torrent cites no evidence whatever to support this argument based on structural similarity. Second, the argument has nothing to do with the Kim reference, contrary to the section heading. Third, the argument glosses over the details of the modification process: it is undisputed that, to change F162 into alogliptin, more needs to happen than replacing the xanthine scaffold with a uracil scaffold. Torrent overlooks that it is still at the starting line, and needs to show that F162u – which is *not* alogliptin – is an obvious modification of F162. This paragraph does not mention F162u. This appears to be a

detour from the key issue of the impact of the Kim reference.

Next is this subheading: "Dr. Rotella Testified About The Need For Constant Drug Discovery As Another Source Of Motivation, Particularly In The Market For Type 2 Diabetes." (Torrent PTB at 24.) The paragraph that follows proposes, generally, that pharmaceutical companies are motivated to develop new drugs, another uncontroversial general proposition. (Id.) The paragraph does contain one citation to Dr. Rotella's testimony that "a large number of drugs . . . have been developed from plant sources," and that it would not be unusual to look at a plant reference to form the basis of drug discovery. (Tr. 119:25-120:9.) This point heads into the neighborhood of the impact of the Kim reference, but says nothing about the motivating impact of the reference itself.

Torrent then states: "Given the constant need for drug discovery in the Type 2 diabetes market, there was ample motivation for a POSA to modify claim 162 of the Feng Patent in view of Kim." (Torrent PTB at 25.) As the discussion so far has made clear, Torrent's brief has not yet demonstrated anything significant about the Kim reference or its impact.

Finally, Torrent's brief turns to the Kim reference, with the vague assertion that "the Kim reference reinforces what was in the prior art." (Torrent PTB at 25.) Torrent provides no explanation or citation for this assertion. Next, Torrent gives a short summary of the Kim reference, which appears to be accurate. (Id.) Then comes some assertions about the Kim reference:

> Dr. Rotella then opined as follows regarding the teachings of Kim—all of which are undisputed: (1) it was known in the prior art that the specific sites on the DPP-IV enzyme where the DPP-IV inhibitor would bind are hydrophobic (i.e., fat loving), (2) of the 3 compounds, i.e., uracil, rutin and asorbic acid, only uracil can be used as a potential scaffold because rutin and asorbic acid are too hydrophilic (i.e., water loving, the opposite of hydrophobic) and would be inappropriate as a

> DPP-IV inhibitor and, therefore, the DPP-IV inhibitor (i.e., uracil) needs to be hydrophobic; (3) the uracil scaffold and the scaffold of claim 162 have similarities; (4) uracil was also known in the prior art as part of a xanthine scaffold to exhibit DPP-IV activity based upon the teachings of both Kanstrup 2003 and Mark 2004. (FF ¶¶ 94, 102-108.)

(Torrent PTB at 25-26.) This quote, including the citations, constitutes the entirety of the details of Defendants' case, in the post-trial brief, about the motivating impact of the Kim reference. FOF paragraph 94 provides an uncontroversial summary of the Kim reference. FOF paragraphs 102 through 108 offer a more detailed exposition of Defendants' argument about the motivating impact of the Kim reference.

In FOF paragraph 102, Torrent first points to the testimony supporting the uncontroversial proposition that pharmaceutical companies are motivated to find novel compounds for drug development. Defendants raise this at a number of points and, while it is uncontroversial as a proposition about commercial pharmaceutical development, the Federal Circuit has made clear that it does not suffice as a statement of motivation to make specific modifications to a compound:

> Amerigen additionally contends that the Board did not give sufficient weight to its theory—presented in a single-sentence footnote to its argument about salt forms of fesoterodine—that a skilled artisan would have been motivated to modify 5-HMT because 5-HMT was patented at the time of invention. However, even accepting, for the sake of discussion, that a patent on 5-HMT would provide a commercial motivation for a skilled artisan to modify 5-HMT, such a motivation would not be sufficient to prove that the claimed compounds would have been obvious. It was Amerigen's burden to show that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. A general motivation to modify 5-HMT based on a prior patent would not suffice, and as we have already explained, Amerigen did not otherwise meet its burden to prove that the specific claimed modifications to 5-HMT would have been obvious. Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious.

Amerigen, 913 F.3d at 1089 (citation omitted). Following Amerigen, the general commercial motivation to develop novel compounds does not suffice to "to show that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention." Id. The validity challengers must prove that the specific claimed modifications would have been obvious.

Torrent then contends: "The POSA would have been motivated to replace the scaffold of the claim 162 compound with the goal of developing a new DPP-IV inhibitor for the treatment of Type 2 diabetes, because 'scaffold replacement' is one of 'a range of strategies' used by medicinal chemists to design and identify novel structures." (FOF ¶ 102.) As the passage from Amerigen just quoted makes clear, this argument does not suffice to show that the prior art suggested making the specific molecular modification of scaffold replacement with uracil. In support, Torrent cites Dr. Rotella's answer to this question about scaffold replacement: "how would a medicinal chemist know how to do this?" (Tr. 35:18-19.) Dr. Rotella answered:

> Well, the fact of the matter is that these in the topic led to a successful drug, and so that's what a medicinal chemist does. You know, you attempt to identify novel structures using a range of strategies, and scaffold replacement is one of them.

(Tr. 35:20-23.) The transcript thus shows that Dr. Rotella did, indeed, opine that scaffold replacement was one of a range of strategies a POSA would employ to identify novel structures. The cited testimony does not adequately support the broad assertion of motivation that Torrent made. Dr. Rotella testified that scaffold replacement was one strategy in a range of strategies. Torrent does not point to any evidence that this range has 2 members, 20, or 200. The word "range," however, indicates that there are more elements than scaffold replacement. What would have motivated the POSA to choose scaffold replacement as the strategy to pursue?

Torrent has offered no support for the proposition that the POSA would have been motivated to choose scaffold replacement to develop a novel compound from F162. Consider this in light of the relevant Federal Circuit standard, already quoted above:

> [T]he question whether the two claimed compounds are 'patentably distinct' implicates the question of obviousness under § 103, which in the chemical context requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success.

Otsuka, 678 F.3d at 1297. Torrent has not yet identified some reason which would have led a POSA to select scaffold replacement to modify F162 to make F162u with a reasonable expectation of success. The cited testimony says no more than that scaffold replacement was one of a "range" of options.

In FOF paragraph 103, Torrent proposes that "one of the most sought scaffold variations" is the move from peptidic to non-peptidic ligands, citing testimony from Dr. Nichols and the Böhm reference. In the testimony cited, however, Dr. Nichols was asked about the Böhm reference and stated that this variation would be "one goal." (Tr. 395:15-19.) Dr. Nichols did not say that it was a preferred variation, or a desirable one, but merely that it was one goal. Torrent also cites to the Böhm reference, which states: "One of the most sought scaffold-variations is of course the move from peptidic ligands to 'small molecules.'" (JTX-0009 at 2.) The problem is that this quote from Böhm suggests that the move from peptidic to non-peptidic ligands is a popular scaffold variation. It does not support the proposition that scaffold replacement is a preferred option among the undefined range just discussed. It is true that, once one has chosen scaffold replacement, Böhm reports that modifying from peptidic to non-peptidic is popular. But there is not yet any evidence offered to support the proposition that the POSA

had a reason to select scaffold replacement from the range of options.

In FOF paragraph 104, Torrent discusses the Kim reference. Torrent states that the Kim reference demonstrated that uracil had antidiabetic activity, which is correct. Then the fog descends: "Because 'uracil is not a novel compound,' the POSA would have been motivated to use uracil to modify the structure, as opposed to starting with using uracil by itself." (Torrent's FOF ¶ 104.) In support, Torrent cites testimony from Dr. Rotella, which says something different:

> Q: Okay. But just to be clear, you're not saying that I'm going to use uracil by itself, just like you wouldn't use Vitamin C by itself, as part of your opinion. Correct?
>
> A: That's correct. Since you're a medicinal chemist and you're looking for a novel compound, uracil is not a novel compound, and so what you'd have to do is modify the structure.

(Tr. 42:7-12.) Dr. Rotella does not here say that the POSA would have been motivated to use uracil to modify the structure of F162; he says that, because uracil is not a novel compound, a POSA would have been motivated to modify uracil, not F162. Nothing in FOF paragraph 104 connects uracil or the Kim reference to scaffold replacement with F162.

In FOF paragraph 105, Torrent presents evidence that, of the three compounds found to have antidiabetic effect in Kim – uracil, rutin, and ascorbic acid – the POSA would have chosen uracil and not either of the others. It concludes the paragraph by citing this testimony from Dr. Rotella:

> And so that's why a person of skill in the art as I have defined it would recognize uracil as a potentially valuable scaffold to explore for treatment -- or for development of novel DPP-IV inhibitors.

(Tr. 43:12-15.) The context for this statement was Dr. Rotella's explanation of why the POSA

would select uracil as a scaffold rather than ascorbic acid or rutin. Dr. Rotella did not, however, explain why a POSA considering scaffold replacement as a way to develop a novel molecule from F162 would have looked to Kim and thought uracil was a candidate with a reasonable expectation of success.

In FOF paragraph 106, Torrent asserts that a POSA would consider uracil as a potential scaffold for novel DPP-IV inhibitors because uracil is a part of xanthine. Torrent cites the testimony of Dr. Rotella that uracil is a part of xanthine. Again, this says nothing about the link to Kim and scaffold replacement. What is it about the structural relationship between xanthine and uracil that would motivate a POSA to replace a xanthine scaffold with uracil?

In FOF paragraphs 107 and 108, Torrent presents evidence for the choice of one of four possible structures for the new molecule with a uracil scaffold. Turning back to Torrent's post-trial brief, the last subsection challenges Takeda's case regarding the Kim reference.

This covers Defendants' case regarding the Kim reference and its role in the first obviousness-type double patenting theory. As stated, Federal Circuit law requires a party seeking to prove invalidity under the doctrine of obviousness-type double patenting, in the chemical context, to identify some reason that would have led a POSA to modify the earlier compound to make the later compound with a reasonable expectation of success. Otsuka, 678 F.3d at 1297. As to the first alternative theory, Defendants have failed to do so: they have not presented evidence to support finding a pathway from F162 to alogliptin under this standard. Defendants identified F162 as the earlier compound, and offered evidence that a POSA would have been motivated to modify F162 to create a novel compound which might be attractive for commercial drug development. It is at this point that the path has a big gap. The evidence of

record shows that scaffold replacement was one of a range of possible strategies for modifying F162 to create a novel compound. Defendants have not offered any evidence that provides a reason why a POSA would have chosen scaffold replacement[4] as a technique for modifying F162, nor evidence that supports finding that a POSA would have had a reasonable expectation of success. Defendants' post-trial brief pointed to no evidence regarding the link to the Kim reference: what would be the reason that a POSA, seeking to modify F162 to create a novel compound, would have looked to the Kim reference? Even if, for purposes of discussion, we accept that a POSA would have known of the Kim reference, there is no evidence or rational explanation for why a POSA would have had a reason to replace the xanthine scaffold with uracil. The Kim reference teaches that uracil, administered orally, had antidiabetic effect in that it was associated with lower blood glucose in an animal model. The '344 patent is directed to

---

[4] Furthermore, Takeda points out that the evidence supports the inference that a POSA would not have had the necessary skills to succeed with scaffold hopping prior to the Priority Date. Dr. Rotella stated that the proposed scaffold replacement technique was the one the Böhm reference called "fragment replacement." (Tr. 76:7-19.) Böhm Table 1 states that this technique may involve noncommercial tools. (JTX-0009 at 5, Table 1.) Dr. Nichols testified that such tools were not available to the POSA. (Tr. 322:20-25.) Asked about such tools, Dr. Rotella stated:

> Q: And you don't know how to use those tools today. Right?
> A: I do not.
> Q: And consequently, the skilled worker in 2004 certainly didn't know how to use them either. Right?
> A: Possibly not, depending --
> Q: Okay.
> A: -- on the level of expertise of that skilled worker.

(Tr. 78:18-25.) This constitutes a concession that the use of such tools would not be within the skill set of a POSA, since not all POSAs would have the expertise to use them. This point alone defeats every scaffold replacement theory offered by Defendants: the POSA did not have the expertise needed to do scaffold replacement before the Priority Date.

DPP-IV inhibitors; F162 is a DPP-IV inhibitor. Defendants did not explain why a POSA interested in developing a novel DPP-IV inhibitor would find relevant or useful a study on compounds associated with lower blood glucose. Nor did Defendants offer even a colorable explanation for why a POSA, reading the Kim reference, would have had a reason to select uracil as a new scaffold for F162. Defendants' first obviousness-type double patenting theory has big holes.

Furthermore, Torrent relies substantially on the testimony of Dr. Rotella, whose credibility was damaged on cross-examination. During the direct examination, Dr. Rotella stated that the substituents of F162 and alogliptin are the same, but the scaffolds differ. (Tr. 32:14-19.) On cross-examination, Dr. Rotella agreed that F162 contained a fluorine atom as a substituent, while alogliptin does not. (Tr. 67:11-18.) Dr. Rotella conceded that, in his previous testimony, he treated the fluorine as part of the scaffold of F162, and he had just agreed to the opposite. (Tr. 67:22-68:7.) This significantly damaged his credibility as an expert witness.

Dr. Rotella's credibility also suffered from inconsistent testimony. He admitted that one could change a single atom of F162 and create a molecule outside the scope of the '344 patent with activity as a DPP-IV inhibitor. (Tr. 107:3-17.) Just previously, Dr. Rotella denied that he said that switching the scaffold of F162 was the simplest way to create a novel compound, and stated that that it would surprise him to learn that, at his deposition, he testified to that; the record showed that he had done so. (Tr. 105:11-23.) Dr. Rotella then stated that switching the scaffold was simpler than switching a substituent. (Tr. 105:24-106:5.) It was after this that he admitted that the change of the single nitrogen would result in a DPP-IV inhibitor outside the

scope of the ’344 patent. This testimony shows important inconsistencies and further damaged Dr. Rotella’s credibility.

2. Torrent’s second ODP theory

Torrent’s post-trial brief next presents the second obviousness-type double patenting theory, based on isosteric replacement. This theory presents an alternative pathway from F162 to alogliptin, and appears[5] to have the following steps: 1) because the fluoro-olefin and amide groups are bioisosteres, substitute an amide group for the fluoro-olefin group, which can be done in two orientations and thus results in molecules A and B; 2) discard molecule B because it contains a nitrogen-nitrogen bond which is pharmaceutically undesirable; 3) improve the hydrophobicity of molecule A by replacing the nitrogen at the bottom of the scaffold with carbon, which results in uracil analogue 1; 4) replace a hydrogen atom with a methyl (CH_3) group, producing alogliptin.

As already discussed, the Court applies the Otsuka standard to this second obviousness-type double patenting theory. Torrent’s post-trial brief has little to say about the key elements of this standard: 1) identifying a reason that would have led a chemist to modify the earlier compound; 2) demonstrating a reasonable expectation of success.

The first step in alternative pathway 2 is the isosteric replacement of a fluoro-olefin group with an amide group. Torrent contends that fluoro-olefin and amide were known in the prior art as isosteres, and there is a factual dispute between the parties on this point. The Court need not resolve this dispute because, even if it resolved the dispute in Defendants’ favor, Torrent’s brief

[5] Torrent’s brief presents no summary statement of the steps in alternative pathway 2, and so the Court has gleaned this summary from the brief and Dr. Rotella’s testimony.

makes no case for the necessary elements of the Otsuka standard: a reason for this modification, and the basis for a reasonable expectation of success. Why would a POSA have decided to perform this replacement? Torrent, in its post-trial brief, argues only that it was known in the art as something that could be done, but that does not provide a reason to do it. Paragraph 111 of Torrent's proposed FOF, however, bears this heading: "Motivation to Replace the Scaffold of the Claim 162 Compound via Isosteric Replacement." FOF paragraphs 111-113 focus on the isosteric replacement decision in alternative pathway 2. These paragraphs largely address the basis for the proposition that the art recognized isosteric replacement of fluoro-olefin and amide bonds. The only statement in these paragraphs that deals with the Otsuka standard is this:

> Because the POSA are medicinal chemists who are "always looking for a novel compound," the POSA would have been motivated to replace the fluoro-olefin in the scaffold of the claim 162 compound with its isostere (an amide bond) with a reasonable expectation to develop a new DPP-IV inhibitor for the treatment of Type 2 diabetes. (Rotella Tr. 42:10-11.)

(Torrent's FOF ¶ 111.) The cited part of Dr. Rotella's testimony is this statement: "Since you're a medicinal chemist and you're looking for a novel compound . . ." (Rotella Tr. 42:10-11.) Thus, Torrent argues only that the search for a novel compound would motivate the decision to replace the fluoro-olefin group with an amide and provide the basis for a reasonable expectation of success. As already established, this is insufficient under Federal Circuit law.

This Court finds that this argument is insufficient as a matter of law to satisfy the requirements of Federal Circuit law under Otsuka. Torrent has pointed to no evidence about the number of possible ways that a chemist could potentially modify F162 to produce a novel compound, but Torrent's arguments reflect that there are at least two (the two strategies that form the basis of theory 1 and theory 2.) Takeda points to the testimony of its expert, Dr. Nichols:

> Q. Now, you heard Dr. Rotella testify about the changes he would have made to the 162 compound. In your view, having considered the changes that Dr. Rotella proposed, do you believe that a skilled artisan could have or would have made different changes?
>
> A. If you were going to change this molecule, you could change it in an almost infinite number of ways.
>
> Q. Explain.
>
> A. So you could change -- there are all kinds of ways you could change this. You could put different aromatic rings here, you could substitute different things here. You could decrease the size of this ring. You could have a straight chain. You could have a piperazine here.

(Tr. 299:13-25.) Dr. Nichols' statement that one could change F162 in an almost infinite number of ways is unrebutted. This Court finds that there were many possible ways to modify F162.

Consider the Federal Circuit's analysis of a similar issue in Eli Lilly & Co. v. Teva Parenteral Meds., Inc.:

> Based on the evidence presented at trial, we discern no error in the district court's findings or its conclusion that the asserted claims are patentably distinct from the '608 Compound. In the chemical context, we have held that an analysis of obviousness-type double patenting "requires identifying some reason that would have led a chemist to modify the earlier compound to make the later compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1297. Here, the district court considered the parties' arguments and evidence, particularly their conflicting expert testimony as to how an ordinarily skilled chemist presented with the '608 Compound would have been motivated to proceed at the time. In its decision, the court credited Lilly's evidence to find that "the ways in which a person of ordinary skill in the art would modify [the '608 Compound] would not result in pemetrexed." *Eli Lilly*, 2011 U.S. Dist. LEXIS 83124, 2011 WL 3236037, at *4. We owe that finding considerable deference on appeal, and we see no clear error based on the record before us. Moreover, a complicated compound such as the '608 Compound provides many opportunities for modification, but the district court did not find that substituting a phenyl group into the aryl position was the one, among all the possibilities, that would have been successfully pursued. Thus, absent

> any motivation to derive pemetrexed from the '608 Compound or reason to expect success in doing so, the district court correctly concluded that the asserted claims were not invalid for obviousness-type double patenting over the '608 Compound.

Eli Lilly & Co. v. Teva Parenteral Meds., Inc., 689 F.3d 1368, 1378 (Fed. Cir. 2012). As in the instant case, at issue was whether a patented compound (pemetrexed) was patentably distinct, within the meaning of the doctrine of obviousness-type double patenting, from a compound in a prior art patent (the '608 Compound). Id. at 1376-77. The Federal Circuit's approach to this issue is instructive. The Federal Circuit applied the Otsuka standard to the issue of obviousness-type double patenting in a chemical context. Id. at 1378. The Federal Circuit held that, because the prior art compound was a "complicated compound" that "provides many opportunities for modification," the district court correctly determined that the proposed modification was not "the one, among all the possibilities, that would have been successfully pursued." Id. The Federal Circuit concluded that the claims at issue were not invalid for obviousness-type double patenting over the prior art compound because the district court had found no motivation to make the modification nor reason to expect success in doing so. Id.

Eli Lilly guides this Court to its decision on the instant question. Here, as in Eli Lilly, the issue is obviousness-type double patenting in a chemical context, and this Court applies the Otsuka standard. Here, as in Eli Lilly, the evidence showed that there were many possibilities for modification of the prior art compound. Here, as in Eli Lilly, the challenger has not demonstrated that one particular modification (substitution of an amide for a fluoro-olefin group) is "the one, among all the possibilities, that would have been successfully pursued." Id. This Court concludes that the asserted claims are not invalid for obviousness-type double patenting over F162, under Defendants' alternative pathway 2.

This analysis applies to not only the first step, but to every step in alternative pathway 2. At no point have Defendants shown that the proposed modification was "the one, among all the possibilities, that would have been successfully pursued." Id. In addition to the fluoro-olefin substitution step, this is true of the third step, wherein the nitrogen at the bottom of the scaffold is replaced with carbon, as well as the fourth step, wherein a hydrogen atom is replaced with a methyl (CH_3) group. Defendants have failed to demonstrate a motivation to make each specific modification as well as a reason to expect success in doing so.

B. Patent invalidity: obviousness under § 103

Indoco filed the post-trial brief asserting Defendants' defense that claims 4 and 12 are invalid as obvious, pursuant to 35 U.S.C. § 103. In summary, the argument entails the following points: 1) a POSA would select DCAX as a lead compound; 2) a POSA would be motivated to replace the xanthine scaffold of DCAX with uracil; and 3) a POSA would be motivated to create the R and S stereoisomers and select the R stereoisomer, resulting in alogliptin. The Court notes that while the scaffold replacement step raises some issues which overlap with the scaffold replacement step in Defendants' first obviousness-type double patenting theory, which also involved replacing a xanthine core with a uracil, Indoco's post-trial brief makes no use of the Kim reference.

The Federal Circuit has set forth these fundamental principles for the determination of obviousness, pursuant to 35 U.S.C. § 103:

> A party seeking to invalidate a patent based on obviousness must prove by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so. The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact. The presence or absence of

a reasonable expectation of success is also a question of fact.

Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd., 923 F.3d 1051, 1059 (Fed. Cir. 2019) (citations omitted). The Federal Circuit employs a lead compound analysis in cases like this one, in which the obviousness of a new chemical compound is in dispute:

> In lead compound cases, the court first determines whether a person of ordinary skill in the art "would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-92 (Fed. Cir. 2012). This requires the patent challenger to show by clear and convincing evidence that a person of ordinary skill "would have had a reason to *select* a proposed lead compound or compounds over other compounds in the prior art." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (emphasis added). The court then determines "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Otsuka*, 678 F.3d at 1292.

Novartis, 923 F.3d at 1060.

In brief, Indoco argues that, prior to the Priority Date, a POSA searching for a promising drug development candidate would have focused on non-peptidic inhibitors and specifically on xanthine-based compounds, which a POSA would recognize as "particularly promising." (Indoco PTB at 16.) Defendants argue that, in short, two references suggest DCAX as lead compound, the WO '496 patent and the CA '730 patent. Defendants point out that DCAX is the first example in the WO '496 patent, and, in the CA '730 patent, DCAX is the fifth most potent compound.[6] Defendants argue that, of the eight compounds mentioned in both the WO '496 and CA '730 patents, DCAX is the most potent.

[6] There is no dispute that the CA '730 patent provided IC_{50} potency values for 31 compounds, and that DCAX was listed as the fifth most potent, with a value of 10 nanomolar, which indicates a potent DPP-IV inhibitor. (JTX-0015 at 102-03; Tr. 410:12-18.)

Plaintiffs contend that Defendants' theory is based on hindsight. Plaintiffs argue that Defendants rely principally on the testimony of their expert, Dr. Ferraris, but that his credibility is undermined by, and is inconsistent with, his own work. Dr. Ferraris testified that peptidic inhibitors were "widely acknowledged," prior to the Priority Date, to have chemical stability issues. (Tr. 142:25-143:2.) Dr. Ferraris also stated that a POSA would have ignored peptidic inhibitors when seeking a lead compound. (Tr. 191:24-192:3.) Dr. Ferraris stated, nonetheless, that he wrote three articles on DPP-IV that came from research he conducted at Guilford Pharmaceuticals during 2001 to 2002. (Tr. 131:9-20.) On cross-examination, Dr. Ferraris acknowledged that his work at Guilford was exclusively on peptidic inhibitors. (Tr. 193:6-20.) Dr. Ferraris agreed that the goal of this work was to find the best inhibitor candidates to develop into a therapeutic product. (Tr. 194:10-19.) Dr. Ferraris stated that he never told his bosses to stop this research and look only at non-peptidic inhibitors (Tr. 195:23-196:1.) Dr. Ferraris agreed that the Wiedeman reference talks a lot about research on peptidic inhibitors, and that a number of companies in 2003-2004 were studying them. (Tr. 191:21-192:13.) Dr. Ferraris published a paper in 2004 about his work exclusively on peptidic inhibitors. (Tr. 193:6-194:1.) Dr. Ferraris stated that he published a 2007 article about this work that favorably described certain peptidic inhibitors he studied. (Tr. 195:5-22.) Thus, while Dr. Ferraris testified that a POSA seeking a candidate for drug development would have ignored peptidic inhibitors, his own work during this time was on peptidic inhibitors, with the avowed goal of finding the best development candidates, and he published one article exclusively on peptidic inhibitors, and another article that stated positive conclusions about certain peptidic inhibitors. His actual work thus contradicts his opinions in this case. These are important inconsistencies which

significantly damaged his credibility as an expert witness. This Court finds that Dr. Ferraris had low credibility as an expert witness.

Next, Plaintiffs point to the fact that Dr. Ferraris admitted that he did not actually do an independent lead compound analysis. (Tr. 189:5-10.) Dr. Ferraris testified that the choice of DCAX and the two references supporting that choice, the WO '496 and CA '730 patents, were given to him by Defendants' counsel; he did not search through the prior art to find them. (Tr. 188:12-189:4.) Given his low credibility, and his admission that he did not survey the prior art, this Court concludes that Dr. Ferraris' testimony about the choice of lead compound should be given little weight. As already established, under Federal Circuit law, this Court inquires whether a POSA would have had a reason to select a proposed lead compound over other compounds in the prior art. Dr. Ferraris admitted that he did not survey the prior art. His opinion that a POSA would have had a reason to select DCAX as lead compound over other compounds in the prior art has inadequate support, and this Court gives it little weight.

Furthermore, Defendants' path to the selection of DCAX is unpersuasive. Defendants argue, in short, that there are eight compounds that are mentioned in both the WO '496 and the CA '730 patents and that, of those eight compounds, DCAX has the greatest potency. Defendants did not explain why a POSA would believe that a compound mentioned in two patents is more worthy of development than a more potent compound listed in one. Furthermore, of the eight compounds mentioned in the two patents, Dr. Ferraris admitted that six had no potency data. (Tr. 221:10-12.) Of the compounds tested for potency in the CA '730 patent, four were more potent than DCAX.[7] Moreover, the CA '730 patent contains a list of 38

[7] In addition, Plaintiffs point to the Mark 2004 reference, which Dr. Ferraris also said a POSA

preferred compounds, and DCAX is not on that list. (JTX-0015 at 88-89; Tr. 214:4-9.) This Court concludes that Defendants have failed to demonstrate that a POSA would have had a reason to select DCAX as lead compound over other compounds in the prior art.

The next step in Defendants' argument is the proposition that a POSA would be motivated to modify DCAX to create a novel compound, one that is not under patent protection and thus commercially attractive as a candidate for development. As has been discussed, this is not a controversial proposition, but it does not suffice as a motivation for the specific molecular modifications that follow in the theory.

Defendants' theory of the motivation for modification of DCAX is not persuasive. Indoco's brief states: "Perhaps the most important reason for a POSA to choose DCAX as a lead compound is because DCAX has two key functional groups that were known to be important to DPP-IV inhibition."[8] (Indoco PTB at 20.) Four pages earlier, however, Indoco's brief states: "Non-peptidic DPP-IV inhibitors, and xanthine-based inhibitors in particular, would be a ripe area for study by a POSA in March 2004."[9] (Indoco PTB at 16.) Immediately after this is a subheading that reads: "A POSA Would Recognize Xanthine Based Compounds As Particularly Promising Based On Large Pharmaceutical Interest And Discovery." Yet, four pages later, Indoco begins the sharp turn away from the promise of xanthine-based inhibitors, and starts to find it obvious to abandon the xanthine base. It is certainly puzzling that Indoco's argument has

---

would have considered, and observe that this reference gives IC_{50} values for 46 compounds, of which 34 were more potent than DCAX. (Tr. 218:16-25.)

[8] This refers to the cyanobenzyl and aminopiperidinyl substituent groups.

[9] On page 11, Indoco's brief states that a POSA would focus specifically on xanthine-based compounds. On page 14, Indoco's brief states: "of the classes of non-peptidic inhibitors disclosed in Wiedeman, a POSA in March 2004 would focus on xanthine based compounds for further review." (Indoco PTB at 14.)

the POSA first attracted to the "particularly promising" xanthine-based inhibitors, but then immediately finds it obvious to get rid of the xanthine.[10] At the very least, this is curious.[11]

Indoco contends that the DCAX molecule can be viewed as having three essential parts: the substituent groups (cyanobenzyl and aminopiperidinyl), and the xanthine scaffold or core. Indoco argues:

> The SAR data in the prior art provides a clear indication of which portions of DCAX should remain unchanged. Modifying DCAX to add or take away substituents groups to the xanthine scaffold would require disturbing the very portions identified as critical to potency. . .
>
> Thus, a POSA would recognize that a clear way to modify DCAX to avoid existing patents would be to change its scaffold.

(Indoco PTB at 29.) As already noted, this represents a sharp turn in Defendants' theory: in the preceding step, the xanthine core was essential, but now the substituent groups have become essential and the xanthine core disposable, and getting rid of it is the way to make a novel compound. Indoco's argument in support is cursory and conclusory. Indoco has no explanation and no evidence, save for Dr. Ferraris' conclusory testimony, for this crucial and surprising turn in the theory.

---

[10] This brings to mind the Federal Circuit's statement in Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd, 533 F.3d 1353, 1358 (Fed. Cir. 2008): "The record, however, shows no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature, the fluorinated substituent, that gave this advantageous property." Similarly, in Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd., 619 F.3d 1346, 1356 (Fed. Cir. 2010), the Federal Circuit cited Eisai and criticized defendant Mylan for selecting a molecule on the basis of a feature, "only to reject that very feature," which is what Indoco has done here.

[11] At points, Indoco makes assertions that contradict other points. On page 26, Indoco's brief argues: "With respect to DCAX, the structural features that would guide a POSA to pick DCAX as a lead compound are the same features that the POSA would certainly keep in optimizing DCAX." (Indoco PTB at 26.) This is contrary to Indoco's theory, which has the POSA choosing DCAX in large part because of the promise of xanthine-based compounds, but then getting rid of the xanthine.

In the middle of this, Indoco's brief makes a key concession: "because DCAX is very potent, a smaller change is better." (Indoco PTB at 27.) In accord with this, Dr. Ferraris testified about DCAX as follows:

> And so as a person of ordinary skill in the art, you would look at this and you would say, okay, the only part I can really modify -- because this is very potent, I don't want to change too much, I just want to change a little, I want to keep as much of that xanthine as possible. So what you would do is you would keep as much atoms as possible . . .

(Tr. 169:5-10.) Then, he testified: "As I mentioned before, DCAX is a very potent lead compound so you don't want to do too much to the central scaffold, so you want to keep as much in place as possible." (Tr. 170:24-171:1.) This testimony supports the concession in the post-trial brief that a POSA would want to change as little as possible, which contradicts Indoco's central contention that it would be obvious to make the major change of scaffold. Furthermore, Dr. Ferraris here stated that he would "want to keep as much of that xanthine as possible," which contradicts the main idea that it would be obvious to replace the xanthine, not keep it.

The proposition that a POSA would be motivated to make smaller rather than larger changes to DCAX appears reasonable and is undisputed, but it constitutes a big problem for the scaffold replacement theory. If a smaller change is better, why not create a novel compound with a tiny change to DCAX? Indoco does not address this issue. Defendants have no basis for their contention that a major change in the molecule would be obvious to the POSA, when, they concede, a tiny one could suffice to yield a novel molecule.[12]

[12] As already noted, Defendants' other expert, Dr. Rotella, admitted this about modifying F162: one could change a single atom, the nitrogen at the bottom of the central ring, and create a molecule outside the scope of the '344 patent with activity as a DPP-IV inhibitor. (Tr. 107:3-17.)

The next step is the proposition that it would be obvious to the POSA to get rid of the xanthine scaffold and substitute a uracil. Indoco offers this explanation: a POSA would recognize that xanthine is a naturally occurring nitrogenous base, of which there are a small number which are considered "privileged structures" for pharmaceutical compounds, and there are fewer than ten such bases. Therefore, use uracil. Indoco provides a cursory explanation of how the POSA went from less than ten of these bases to just one, uracil. Indoco contends: 1) a POSA would view uracil and xanthine as similar in chemical structure; and 2) xanthine is a two-ring structure, while uracil is a one-ring structure, and moving to a one-ring structure would be a way to increase solubility, which is always good.

Indoco has offered a very cursory explanation for this essential proposition – that it would be obvious to the POSA to swap uracil for xanthine in the search for novel compounds. Conspicuously absent is anything about the competing candidates from the small group of naturally occurring nitrogenous bases. Indoco says only that there are less than ten of them, so perhaps there are seven possible bases that are not xanthine or uracil. There is no explanation of the selection of uracil as the obvious choice over the others. There is a throwaway line in the brief that it would be obvious to try this limited group of options and test the outcome, with a citation to KSR. Other than a single sentence in the post-trial brief, there is no discussion of this idea.

In the next step in the argument, Indoco contends that the POSA would have a reasonable expectation of success in swapping the xanthine core of DCAX for uracil. The subsection on this key point in Indoco's post-trial brief contains three paragraphs, and two are only quotes from cases. The last paragraph, which contains the analysis and the argument, is quoted here in its

entirety:

> It is undisputed that the DCAX and alogliptin have significant structural similarity. FOF ¶ 305. The functional groups responsible for DPP-IV inhibition in DCAX and alogliptin are identical and, as the totality of the prior art indicates, the scaffolds of both DCAX and alogliptin are naturally occurring nitrogenous bases which can be commonly switched out for one another. FOF ¶¶ 220, 305.

(Indoco's PTB at 35.) Paragraph 220 in Indoco's FOF deals with the interchangeability of naturally occurring nitrogenous bases and does not speak to the expectation of success with this particular scaffold replacement. Paragraph 305 is in the "Conclusions of Law" section and contains only proposed conclusions of law, not citations to evidence. Indoco's post-trial brief cites no evidence to support the assertion that a POSA would have had a reasonable expectation of success with this modification of DCAX.

The first sentence of this paragraph alleges "significant structural similarity," which appears to connect to a case quote in the previous paragraph: "It is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship ... to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." Otsuka, 678 F.3d at 1292. Applying this principle, the factual question is whether DCAX and alogliptin possess a sufficiently close relationship to create an expectation that the new compound will have similar properties to the old. It would seem that the best evidence of the state of such facts would come from expert testimony, but Indoco has pointed to none, instead relying on the unsubstantiated assertion that it is undisputed that DCAX and alogliptin have significant structural similarity. It is correct that there is no dispute that DCAX and alogliptin share the cyanobenzyl and aminopiperidinyl groups as substituents. Is this similarity sufficient to constitute a sufficiently close relationship to create the expectation that

the new compound will have similar properties to the old, as Otsuka requires? This would appear to be a question with two components. First, what is the nature of the structural similarity between DCAX and alogliptin, a question best answered by the experts. Second, how does Federal Circuit law define sufficient structural similarity?

As to the second question, the Federal Circuit addressed it in Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed. Cir. 2007):

> We elaborated on this requirement in the case of *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.

Thus, pursuant to Takeda, a "known compound may suggest its homolog, analog, or isomer." Id. There is no evidence that DCAX and alogliptin are homologs, analogs, or isomers.

As to the expectation of success from scaffold replacement, Defendants do not point to expert testimony on the subject, but Plaintiffs' expert, Dr. Nichols, was asked directly about the expectation of success with scaffold replacement:

> Q. Do you have a view as to whether a person of ordinary skill in the art in March 2004, were they to try to change a pyrimidone on scaffold and uracil scaffold wholesale, as Dr. Rotella suggested, do you believe a person of ordinary skill in the art would be able to predict the resulting properties of the compound?
>
> A. No, absolutely not.

(Tr. 310:23-311:4.) Although this exchange appeared in the context of a discussion of Dr.

Rotella's testimony, not Dr. Ferraris', it is a direct question and a direct answer about whether a POSA could predict the resulting properties of the compound after scaffold replacement of xanthine with uracil. This testimony is unrebutted. This Court finds that a POSA replacing a xanthine scaffold with a uracil would not be able to predict the resulting properties of the compound. Thus, even apart from the question of whether the prior art would have supplied a POSA with a reason to modify DCAX by substituting a uracil scaffold, Defendants have failed to show that a POSA who did so would have a reasonable expectation of success.

The Court has not here discussed every detail of Indoco's § 103 obviousness argument and need not do so. The argument has a number of major gaps, missing connections or steps with inadequate support. This is a theory with major defects and does not come close to meeting the clear and convincing standard for successful validity challenges.

Defendants' obviousness theories show the operation of hindsight, and bring to mind the Federal Circuit's obviousness assessment in Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008):

> In other words, Mylan's expert, Dr. Anderson, simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious. Of course, this reasoning is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine "the subject matter as a whole" to ascertain if it "would have been obvious at the time the invention was made." 35 U.S.C. § 103(a).

In the instant case, as in Ortho, the experts consistently discounted – or, more often, completely ignored – the number and complexity of the alternatives. And both of Defendants' experts openly admitted the role of hindsight in their reasoning. For example, Dr. Ferraris was asked about some deposition testimony:

> Q: I asked you:
> (Reading) But for the purpose of the analysis that you undertook here, you were thinking of a POSA whose only interest was to develop a DPP-IV inhibitor. Is that fair?
> That's fair.
> QUESTION: Any kind of DPP-IV inhibitor?
> ANSWER: No.
> QUESTION: What kind?
> The kind that had the path of least resistance.
> Keep going, please.
> QUESTION: What does that mean? Path of least resistance between what and what?
> That means the lead and the final compound, the final drug.
> The final drug in this case being alogliptin?
> Your answer: "Correct."
> Did I ask you those questions and you gave those answers under oath, sir?
> A: That is correct.

(Tr. 189:24-190:17.) This shows that, at the deposition, Dr. Ferraris admitted that he was trying to find the path of least resistance between the lead compound and alogliptin, which is working backward from the invention; it is hindsight.

Dr. Rotella also admitted the use of hindsight in testimony at his deposition, which was presented to him at trial:

> Q: And the Judge asked -- and I refreshed your recollection with some deposition testimony which we'll put up on the screen, where I asked you: "Would a bigger alkyl group potentially occupy the S2 site better than methyl?" And your answer was: "I don't have any information about the structure - activity relationships in that case. However, adding a methyl group simply gets you, as indicated, from compound 1 to alogliptin." I asked you that question and under oath you gave that answer. Correct?
> A: Yes.

(Tr. 104:2-13.) This is an open admission that Dr. Rotella also worked backward from the invention, using hindsight.

The Court concludes that Defendants have failed to prove, by clear and convincing evidence, that claims 4 and 12 of the '689 patent are invalid under their theories based on § 103

obviousness or the doctrine of obviousness-type double patenting. Pursuant to 35 U.S.C. § 282(a), a patent is presumed valid, and the burden of establishing invalidity rests on the party asserting it. Claims 4 and 12 of the '689 patent are presumed valid, and Defendants have not met their burden of establishing invalidity by clear and convincing evidence. The parties have stipulated to a finding that claims 4 and 12 are infringed. This Court determines that claims 4 and 12 of the '689 patent are valid and infringed. Judgment will be entered in favor of Plaintiffs on their claims that the proposed ANDA products infringe claims 4 and 12 of the '689 patent.

Pursuant to FED. R. CIV. P. 52(a), the Court presents its findings of fact and conclusions of law.

FINDINGS OF FACT

I. This Opinion incorporates by reference all stipulated facts set forth in the Final Pretrial Order.

II. Based on the evidence presented at trial, this Court now makes the following findings of fact:

1. The '689 patent descends from provisional application No. 60/553,571, filed on March 15, 2004 (the "Priority Date.")

2. The relevant art of pharmaceutical development, as of the Priority Date, understood that very small changes in molecular structure could have dramatic effects on the biological properties of the molecule. As a result, the impact of even a small change in molecular structure on the biological properties of the modified molecule was difficult to accurately predict.

3. As of the Priority Date, successful use of the technique of scaffold hopping required the availability of a template, a chemical structure displaying the desired biological activity.

4. To a POSA seeking to create a non-peptidic inhibitor of the DPP-IV enzyme, the desired biological activity would have been the binding of the non-peptidic molecule to the DPP-IV receptor site.

5. As of the Priority Date, the art did not have available a crystal structure of a non-peptidic molecule bound to the DPP-IV receptor site.

6. As of the Priority Date, the art did not have available a chemical structure of a non-peptidic molecule that was active as a DPP-IV inhibitor.

7. As of the Priority Date, the art did not have available the structural information needed to perform scaffold replacement to produce a non-peptidic molecule that was active as a DPP-IV inhibitor with a reasonable expectation of success.

8. Employees of pharmaceutical companies are motivated to find novel compounds for drug development.

9. There were many possible ways to modify the F162 molecule.

10. The prior art Kim reference described research which found that administration of oral uracil was associated with lowered blood glucose in an animal model. The Kim reference did not mention DPP-IV or DPP-IV inhibitors or scaffold hopping or the use of uracil as a scaffold.

11. Defendants did not explain how a POSA, seeking to modify F162 to create a novel DPP-IV inhibitor, would go about doing so. Defendants did not offer a theory which contained the options available to the POSA at each step, nor why the POSA would choose one option as the obvious choice at each step.

12. A substitution of a single nitrogen atom in the F162 molecule with a carbon atom would result in a DPP-IV inhibitor outside the scope of the ’344 patent.

13. Defendants did not offer evidence of the range of modification options a POSA, seeking to create a novel DPP-IV inhibitor from F162, would consider, nor what would make the isosteric replacement of a fluoro-olefin group with an amide group the obvious choice.

14. Defendants did not explain how the Kim reference would have persuaded a POSA seeking to create a novel DPP-IV inhibitor from F162 to perform scaffold hopping which swapped the xanthine base with uracil, as the obvious choice out of all possible options.

15. Defendants did not offer evidence of the range of modification options a POSA, seeking to create a novel DPP-IV inhibitor from F162, would consider, nor what would make scaffold hopping the obvious choice.

16. As of the Priority Date, a POSA would not have had the expertise to successfully

perform scaffold hopping.

17. As of the Priority Date, a POSA would not have been motivated to modify F162 by scaffold replacement of the xanthine core with a uracil core.

18. As of the Priority Date, a POSA would not have had a reasonable expectation of success in modifying F162 by scaffold replacement of the xanthine core with a uracil core.

19. The prior art did not supply a POSA with a reason or motivation to modify F162 by scaffold replacement of the xanthine core with a uracil core.

20. The prior art did not supply a POSA with a reason or motivation to modify F162 by isosteric replacement of the fluoro-olefin group with an amide group.

21. As of the Priority Date, a POSA would not have been motivated to modify F162 by isosteric replacement of the fluoro-olefin group with an amide group.

22. As of the Priority Date, a POSA would not have had a reasonable expectation of success in modifying F162 by isosteric replacement of the fluoro-olefin group with an amide group.

23. The CA ’730 patent reported IC_{50} potency values, which show potency as a DPP-IV inhibitor, for 31 compounds, and DCAX was the fifth most potent, with a value of 10 nanomolar. The CA ’730 patent contained a list of 38 preferred compounds, and DCAX was not on that list. The Mark 2004 reference reported potency values for 46 compounds, of which 34 were more potent than DCAX.

24. The prior art recognized xanthine-based compounds as promising for development as DPP-IV inhibitors.

25. The prior art did not supply a POSA with a reason to select DCAX as a lead compound over other compounds in the prior art.

26. Defendants did not explain the range of modification options a POSA, seeking to create a novel DPP-IV inhibitor from DCAX, would consider, nor what would make scaffold hopping the obvious choice.

27. Defendants did not explain why a POSA would consider xanthine-based compounds as promising for development as DPP-IV inhibitors, but then choose to get rid of the xanthine core.

28. A POSA would have believed DCAX to be a very potent molecule as a DPP-IV inhibitor, and would have believed that a smaller change to the structure is better,

for the purpose of preserving that potency. The POSA would have wanted to keep as much of the central scaffold in place as possible.

29. Defendants did not offer evidence that replacement of the xanthine scaffold with a uracil scaffold kept as much of the central scaffold in place as possible.

30. Defendants did not explain why a POSA who had decided to use scaffold replacement to modify DCAX would select uracil over the other naturally occurring nitrogenous bases.

31. The prior art did not supply a POSA with a reason or motivation to modify DCAX by scaffold replacement of the xanthine core with a uracil core.

32. As of the Priority Date, a POSA would not have been motivated to modify DCAX by scaffold replacement of the xanthine core with a uracil core.

33. As of the Priority Date, a POSA would not have had a reasonable expectation of success in modifying DCAX by scaffold replacement of the xanthine core with a uracil core.

CONCLUSIONS OF LAW

1. This Court has jurisdiction over this case pursuant to 28 U.S.C. § 1331.

2. The parties accept this Court's personal jurisdiction.

3. Venue is proper in this district pursuant to 28 U.S.C. § 1391(b).

4. "A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282.

5. The parties stipulated to infringement of claims 4 and 12 of the '689 patent.

6. A POSA, as of the Priority Date, would not have been able to predict the biological properties of F162 after modification by scaffold replacement, and Defendants have failed to demonstrate that the POSA would have had a reasonable expectation of success in doing so.

7. A POSA, as of the Priority Date, would not have found it obvious to modify F162 through scaffold replacement.

8. A POSA, as of the Priority Date, would not have found it obvious to modify F162 through the isosteric replacement of a fluoro-olefin group.

9. A POSA, as of the Priority Date, would not have been able to predict the biological properties of F162 after modification by isosteric replacement of a fluoro-olefin group, and Defendants have failed to demonstrate that the POSA would have had a reasonable expectation of success in doing so.

10. A POSA, as of the Priority Date, would not have found it obvious to select DCAX as a lead compound for further development.

11. A POSA, as of the Priority Date, would not have found it obvious to modify DCAX through scaffold replacement.

12. A POSA, as of the Priority Date, would not have been able to predict the biological properties of DCAX after modification by scaffold replacement, and Defendants have failed to demonstrate that the POSA would have had a reasonable expectation of success in doing so.

13. Defendants have failed to demonstrate, by clear and convincing evidence, that alogliptin was an obvious modification of F162.

14. Defendants have failed to demonstrate, by clear and convincing evidence, that alogliptin was an obvious modification of DCAX.

15. Defendants have failed to demonstrate, by clear and convincing evidence, that claims 4 or 12 of the ’689 patent are invalid as obvious, pursuant to 35 U.S.C. § 103.

16. Defendants have failed to demonstrate, by clear and convincing evidence, that claims 4 or 12 of the ’689 patent are invalid as obvious, pursuant to the doctrine of obviousness-type double patenting.

17. Claims 4 and 12 of U.S. Patent No. 7,807,689 are valid patent claims.

18. Defendants’ ANDA products infringe claims 4 and 12 of the ’689 patent.

An appropriate Order follows.

s/ Stanley R. Chesler
Stanley R. Chesler, U.S.D.J.

Dated: February 4, 2020